[ORIGINAL RESEARCH]

# A New Proprietary Onion Extract Gel Improves the Appearance of New Scars

## A Randomized, Controlled, Blinded-investigator Study

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## ABSTRACT

**Objective:** This randomized, controlled, single-blind study evaluated the appearance of new dermal scars after eight weeks of once-daily application of a nonprescription proprietary onion extract gel formulation compared to control (no application scars) in a dermatological surgical setting. **Methods:** At Visit 1, 44 healthy male and female subjects aged 18 to 70 years gave informed consent, were screened, and enrolled in the study. Two bilateral, 8mm seborrheic keratoses, one on the right and one on the left chest, were surgically removed from each subject. The wounds were photographed at all visits. Two weeks later (Visit 2), each subject was randomly assigned to apply onion extract gel to either the right or left side wound site once daily for eight weeks and no treatment on the opposite wound. The investigator was blinded to which wound was treated. At two, four, and eight weeks after gel application, right and left scars were graded by the investigator and subjects for improvement from baseline in overall appearance, texture, redness, and softness using 4-point ordinal scales (0=no improvement, 1=mild improvement; 2= moderate improvement; 3=significant improvement). Safety was evaluated by adverse events. **Results:** Six subjects (13.6%) experienced mild stinging that resolved spontaneously. At two weeks, the subjects rated gel-applied scars to be significantly softer than control scars ($p$=0.014). After four and eight weeks of application, the investigator and subjects rated all appearance variables of the gel-applied scars to be significantly more improved from baseline than control scars ($p$=0.017 to $p$<0.01). **Conclusion:** The new proprietary onion extract gel is safe and significantly improves scar appearance after four weeks of once-daily application.

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Rapid wound healing without noticeable scarring is an important aspect of cosmetic dermatology. Dermal wounds occur intentionally as a result of surgical procedures or accidentally from skin injury. In either case, both physician and patient desire to see optimal wound healing with minimal scar formation. Accordingly, any scientifically sound pharmacological or physical intervention that can improve scar cosmesis is of significant value.

Dermal scar formation during wound healing is a highly complex genetic process involving disorganized fibrotic deposition of extracellular collagen matrix and inflammatory cell infiltration.[1] Although animal dermal scar models have advanced understanding of the mechanisms of scar formation, safe, effective treatment modalities to prevent or significantly reduce dermal scarring have yet to be developed.[1,2] Existing treatments for improving scar appearance, such as laser therapies, dermabrasion techniques, silicone gel sheeting, and hyaluronic acid, have been utilized with varying degrees of success, but can be unreliable and unpredictable.[2]

There are commercially available botanical agents that improve the appearance of surgical scars.[3,4] One such product is onion (*Allium cepa*) extract, which contains several unique bioflavenoids, such as quercitin, kaempferol, and cepalin; metalloproteinases; and thiosulfates.[5–10] A proprietary consumer-available aqueous onion extract

**DISCLOSURE:** Drs. Draelos and Baumann were clinical investigators in this study and are both paid consultants for Merz Pharmaceuticals, LLC. Drs. Avakian, Plaum, Fleischer, and Hardas are all employees of Merz Pharmaceuticals, LLC. Support for this study was provided by Merz Pharmaceuticals LLC, Greensboro, North Carolina.

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**TABLE 1. Investigator's ratings of scar appearance improvement from baseline after two and four weeks of gel application**

| VARIABLE | ONION EXTRACT GEL | CONTROL | DIFFERENCE (GEL–CONTROL) | *p*-VALUE[a] |
|---|---|---|---|---|
| **Study Week 4** | | | | |
| Overall appearance | 1.20 (0.59) | 1.00 (0.74) | 0.20 (0.88) | *p*=0.064 |
| Texture | 1.13 (0.63) | 0.90 (0.77) | 0.23 (0.94) | *p*=0.058 |
| Redness | 1.13 (0.66) | 0.97 (0.73) | 0.16 (0.86) | *p*=0.113 |
| Softness | 1.25 (0.61) | 1.02 (0.76) | 0.23 (0.89) | *p*=0.048 |
| **Study Week 6** | | | | |
| Overall appearance | 1.68 (0.63) | 1.36 (0.53) | 0.32 (0.96) | *P*=0.017 |
| Texture | 1.70 (0.63) | 1.34 (0.52) | 0.36 (0.94) | *P*=0.007 |
| Redness | 1.68 (0.67) | 1.38 (0.57) | 0.30 (0.95) | *P*=0.023 |
| Softness | 1.70 (0.66) | 1.38 (0.57) | 0.32 (0.96) | *P*=0.017 |

Values are mean (SD) improvement scores from baseline (n=44 subjects). Data for two subjects were imputed by LOCF.
[a]From non-parametric Mann-Whitney one-sided *t*-test for changes in applied vs. control sides at Weeks 4 and 6.
*P*-values <0.025 are significant

cream formulation (Mederma®, Merz Pharmaceuticals, LLC, Greensboro, North Carolina) has been shown to be beneficial for promoting scar smoothness and improving the appearance of new surgical scars when applied three times daily for 2 to 3 months.[11,12]

A more concentrated, advanced, onion extract gel formulation (Merderma® Advanced Scar Gel; Merz Pharmaceuticals, LLC) has recently been developed and will be available in early 2012. This new formulation provides the advantage of requiring one application per day rather than 2 to 3 times per day. The objective of this randomized, controlled, single-blind study was to clinically evaluate the safety and benefit of eight weeks of once-daily application of advanced onion extract gel for improving the overall appearance, texture, color (redness), and softness of new dermal scars in a dermatological postsurgical setting.

## METHOD

**Subjects.** This was a 10-week, randomized, investigator-blinded study in 44 healthy adult volunteer male and female subjects who were seeking treatment for removal of seborrheic keratoses. The study protocol, amendments, and informed consent forms were approved by the Western Institutional Research Board, and the study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) standards. All subjects provided voluntary signed, informed consent and Health Insurance Portability and Accountability Act (HIPPA) authorization prior to screening. To participate in the study, subjects had to be a male or nonpregnant female between 18 and 70 years of age with Fitzpatrick skin type 1 to 6; have at least two 8mm diameter, bilateral, symmetrical seborrheic keratoses on the right and left chest; understand the requirements of the study; and be willing and able to abide by the study restrictions, apply the onion extract gel as instructed, return for the required study visits, and be free from any clinically significant disease that might interfere with study procedures, data measurement, or interpretation. Study exclusion criteria included the following: any known allergies or sensitivities to ingredients contained in the test product including onion extract and lidocaine + epinephrine; known history of keloids or hypertrophic scars; excessive exposure to sunlight; pregnancy (confirmation by urine pregnancy testing); history of any dermal resurfacing procedures or noninvasive skin-tightening procedures, such as Thermage (medium/deep chemical peel, dermabrasion/microdermabrasion treatments) or laser therapy for eight weeks prior to Visit 1 and for the duration of the study; no continuous or intermittent use of systemic or topical corticosteroids; and any irritating topical pigmenting agents applied in the area for two weeks prior to Visit 1 and for the duration of the study.

**TABLE 2. Investigator's ratings of scar appearance improvement from baseline after eight weeks of gel application**

| VARIABLE | ONION EXTRACT GEL | CONTROL | DIFFERENCE (GEL–CONTROL) | *p*-VALUE[a] |
|---|---|---|---|---|
| **Eight weeks** | | | | |
| Overall appearance | 2.59 (0.72) | 2.11 (0.65) | 0.48 (0.95) | *P*<0.01 |
| Texture | 2.61 (0.68) | 2.09 (0.67) | 0.52 (0.93 | *P*<0.01 |
| Redness | 2.61 (0.72) | 2.11 (0.68) | 0.50 (0.90) | *P*<0.01 |
| Softness | 2.61 (0.72) | 2.16 (0.68) | 0.45 (1.02) | *P*<0.01 |

Values are mean (SD) scores for improvement from baseline (n=44 subjects). Data for two subjects were imputed by LOCF.
[a] From non-parametric Mann-Whitney one-sided *t*-test for changes in applied vs. control sides at Week 10.
*P*-values <0.025 are significant

**Procedures.** The study consisted of five vists. At Visit 1, subjects provided informed written consent, were screened (medical history, dermatological examination), and enrolled in the study. The two selected seborrheic keratoses, one on the right and one on the left anterior chest were anesthetized with 2% lidocaine + epinephrine, removed by a scalpel shave, and photographed after bleeding had stopped. Photographs were taken of the wound sites at all visits. The wounds were treated with topical bacitracin and bandaged, and the subjects were instructed to return in two weeks. At Visit 2, subjects whose wounds had healthy granulation tissue were randomly assigned to one of the following two groups: 1) eight weeks, once-daily onion extract gel application to the right chest scar and no application to left chest scar (control) or 2) eight weeks, once-daily onion extract gel appliction to the left chest scar and no application to right chest scar (control). The randomization schedule was provided by the sponsor and administered by the research coordinator. The investigator was blinded to which scar was treated with gel or no gel throughout the study. The initial application of onion extract gel was completed on the appropriate assigned right or left wound. The subjects were instructed to avoid manipulation of the untreated scar and to return for follow up in two weeks (study Week 4), four weeks (study Week 6 ), and eight weeks (study Week 10).

At the follow-up visits, right and left scars were photographed, examined by the subjects and investigator, and graded for improvement from baseline in 1) overall appearance, 2) texture, 3) redness, and 4) softness using separate 4-point ordinal scales (0=no change, 1=mild improvement, 2=moderate improvement, 3=significant improvement). Safety was assessed by the incidence and severity of adverse events throughout the study. The subjects were instructed to maintain a daily diary for both right and left chest scars and specifically note any erythema, scaling, dryness, edema, stinging/burning, discoloration, oozing, crusting, or vesiculation.

**Statistical analysis.** The endpoints were the blinded investigator's and subjects' mean ratings of improvement from baseline in the four appearance variables of the gel-applied and no gel (control) scars after two, four, and eight weeks of application (study Week 10). Any missing data was imputed based on Last Observation Carried Forward (LOCF). Values for improvement scores of each variable at 2, 4, and 8 weeks of application were summarized descriptively and nonparametric Mann-Whitney paired one-sided *t*-tests (Wilcoxon signed-rank test) between mean values for applied and unapplied scars were performed for each visit with a significance level of 0.025.

## RESULTS

**Demographics and subject disposition.** A total of 44 subjects (32 female and 12 male) were enrolled in the study and randomized, and 42 completed the study. Two subjects did not have data from the Week 10 visit and values were imported using LOCF. The subjects' average (range) age was 57 (41–68) years; 39 (87%) subjects were Caucasian, 4 (9%) were African American, and one was Hispanic; 16 (36%) were Fitzpatrick skin type 1, 22 (50%) were type 2, and 2 each were type 3, type 4, and type 5.

**Investigator improvement assessments.** Table 1 presents means and standard deviations (SD) of the investigator's improvement scores for gel-applied and control scars at two, four, and eight weeks of gel application. After two weeks of application (study Week 4), investigator improvement ratings for the applied scars were all higher than for control scars, but the differences were not statistically significant. After four weeks of onion extract gel application (study Week 6), mean improvement scores for the four appearance variables were statistically significantly higher in the gel-applied scars than in control scars (overall

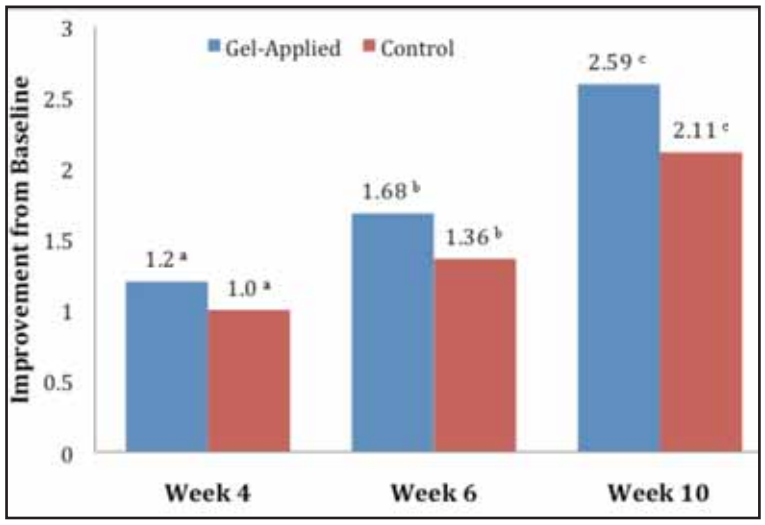


**Figure 1.** Investigator-rated improvement scores for overall appearance of extract gel-applied and control scars after two, four, and eight weeks of daily application.
[a] $p$=0.058; [b] $P$=0.017 ; [c] $P$<0.01; Note: Week 4 = two weeks of gel application

**TABLE 3. Subject-rated improvement in scar appearance from baseline after two weeks and four weeks of gel application**

| VARIABLE | ONION EXTRACT GEL | CONTROL | DIFFERENCE (GEL–CONTROL) | $p$-VALUE[a] |
|---|---|---|---|---|
| **Two weeks** | | | | |
| Appearance | 1.59 (0.89) | 1.29 (1.02) | 0.30 (1.11) | $p$=0.052 |
| Texture | 1.47 (0.95) | 1.11 (1.03) | 0.36 (1.16) | $p$=0.034 |
| Redness | 1.43 (0.92) | 1.13 (0.97) | 0.30 (1.07) | $p$=0.047 |
| Softness | 1.36 (0.94) | 1.00 (1.01) | 0.36 (1.04) | $p$=0.014 |
| **Four weeks** | | | | |
| Appearance | 1.93 (0.94) | 1.36 (1.10) | 0.57 (1.11) | $p$<0.01 |
| Texture | 1.75 (1.05) | 1.10 (1.06) | 0.57 (1.00) | $p$<0.01 |
| Redness | 1.72 (0.97) | 1.27 (1.12) | 0.45 (1.10) | $p$<0.01 |
| Softness | 1.77 (1.03) | 1.25 (1.08) | 0.52 (1.11) | $p$<0.01 |

Values are mean (SD) improvement scores from baseline (n=44 subjects)
$P$-values <0.025 are significant
[a] From non-parametric Mann-Whitney one-sided $t$-test for changes in applied vs. control sides at Weeks 4 and 6

**TABLE 4. Subject-rated improvement in scar appearance after eight weeks of gel application**

| VARIABLE | ONION EXTRACT GEL | CONTROL | DIFFERENCE (GEL–CONTROL) | $p$-VALUE[a] |
|---|---|---|---|---|
| **Eight weeks** | | | | |
| Overall Appearance | 1.97 (0.95) | 1.45 (1.02) | 0.52 (1.07) | $p$<0.01 |
| Texture | 1.88 (1.01) | 1.20 (1.04) | 0.68 (1.05) | $p$<0.01 |
| Redness | 1.93 (0.99) | 1.41 (1.06) | 0.52 (1.15) | $p$<0.01 |
| Softness | 1.82 (1.10) | 1.34 (1.09) | 0.48 (0.95) | $p$<0.01 |

Values are mean (SD) improvement scores from baseline (n=44 subjects)
$P$-values <0.025 are significant
[a] From non-parametric Mann-Whitney one-sided $t$-test for changes in applied vs. control sides at Week 10

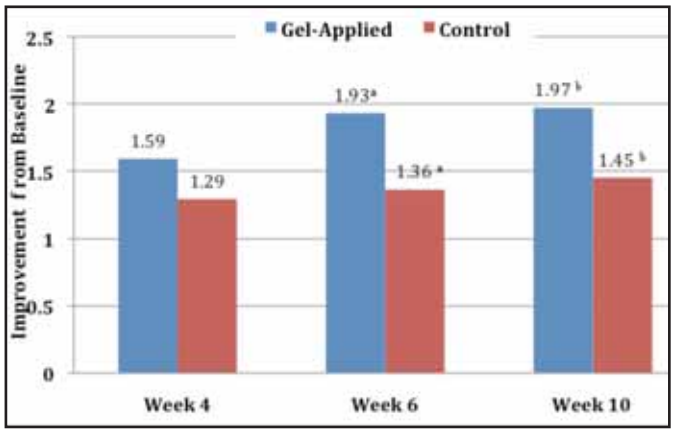


**Figure 2.** Subject-rated mean improvement scores for overall appearance of gel-applied and control scars after two, four, and eight weeks of daily application
[a,b] $p<0.01$; Note: Week 4 = two weeks of application; Week 6 = four weeks of application; Week 10 = eight weeks of application

appearance, $p=0.017$; texture, $p=0.007$; redness, $p=0.023$; softness, $p=0.017$).

Means (SD) of investigator-rated improvement scores for the four appearance variables at Week 8 (study Week 10) in extract gel-applied and control scars are shown in Table 2. For gel-applied scars, the mean improvement score at Week 10 was 2.59 for overall appearance and 2.61 for each of the other variables. For control scars the mean improvement scores from baseline were 2.11, 2.09, 2.11, and 2.18 for overall appearance, texture, redness, and softness, respectively. The difference in mean improvement scores between gel-applied and control scars for each variable was statistically significant at $p<0.01$.

Vertical bars in Figure 1 are mean scores for overall appearance in gel-applied scars and control scars after two, four, and eight weeks of onion extract application, as assessed by the blinded investigator.

**Subjects' improvement assessment.** After two weeks of gel application, the subjects' rating of softness in gel-applied scars was 1.36 (0.94) versus 1.00 (1.01) in control scars ($p=0.014$) (Table 3). Improvement ratings for the other appearance variables were higher in gel-applied scars compared to control scars, but the differences were not statistically significant. After four weeks of application (study Week 6), subject-rated mean improvement scores for the four appearance variables were all significantly higher in gel-applied scars compared to scores for control scars ($p<0.01$) (Table 3).

The subject ratings of improvement from baseline in the appearance of gel-applied and unapplied scars after eight weeks paralleled those of the blinded investigator, but absolute values as assessed by the subjects for each variable were lower overall by 0.5 to 0.8 grade (Table 4). Mean improvement scores for all appearance variables from baseline to eight weeks were significantly higher in onion extract gel-applied scars than control scars ($p<0.01$). The minimum mean increase from baseline for the gel-applied scars was 1.82 for softness and the maximum was 1.97 for overall appearance. The minimum mean change from baseline in the control scars was 1.20 for texture and the maximum change was 1.45 for overall appearance.

Figure 2 graphs subject-assessed mean scores for improvement from baseline in overall appearance of onion extract gel-applied and control scars after two, four, and eight weeks of gel application.

Figure 3 shows photographs from subject #27, representative of progressive improvement in appearance in the extract gel-applied scar on the right and control scar on the left. Figure 3A shows post-surgery wounds and 3B was taken two weeks after surgery prior to application. Figure 3C was taken after four weeks of treatment (study week 6) and 3C was taken after eight weeks of treatment (study week 10).

**Safety.** Onion extract gel was well tolerated. Six (13.6%) of 44 subjects experienced itching, burning, stinging, or contact dermatitis at the site of application, which was probably related to treatment. All events were mild in severity and resolved spontaneously. No subject discontinued use of the product or the study due to adverse events.

## DISCUSSION

The distinct differences in appearance between control scars and onion extract gel-applied scars seen in the photographs of Subject #27 are representative of the majority of subjects (Figure 3). The blinded investigator and subjects both rated overall appearance, texture (smoothness), redness, and softness of the gel-treated scars to be statistically significantly more improved from baseline appearance than in the control scars after four and eight weeks of application. The photograph results combined with the blinded investigator's and subjects' assessments provide good evidence that once-daily application of a proprietary onion extract gel formulation for eight weeks significantly improves the appearance of new dermal scars.

The subjects also assessed the gel-applied scars to be significantly softer than control scars after only two weeks of gel application. From a statistical viewpoint , the objectivity and validity of subject self-rating scales for assessing improvement differences between groups in this type of study is questionable since the subjects were not blinded to treatment and were therefore biased. However, subject self-scoring of aesthetic responses in cosmeceutical studies is a useful tool and provides meaningful information from the viewpoint of consumer/customer satisfaction with the aesthetic outcome of a cosmetic dermatological treatment or product.

The present findings are consistent with the majority of published data on onion extract and scar appearance. Over the past decade, numerous studies have shown that onion extract applied 2 to 3 times a day for periods of 3 to 6 months significantly improves the appearance of postsurgical scars, adhesions, stretch marks, and hypertrophic scars *in vitro* and *in vivo*.[11–20] The weight of evidence from these studies and the present data support the claim that onion extract is beneficial in reducing the appearance of new dermal scars when used as directed.


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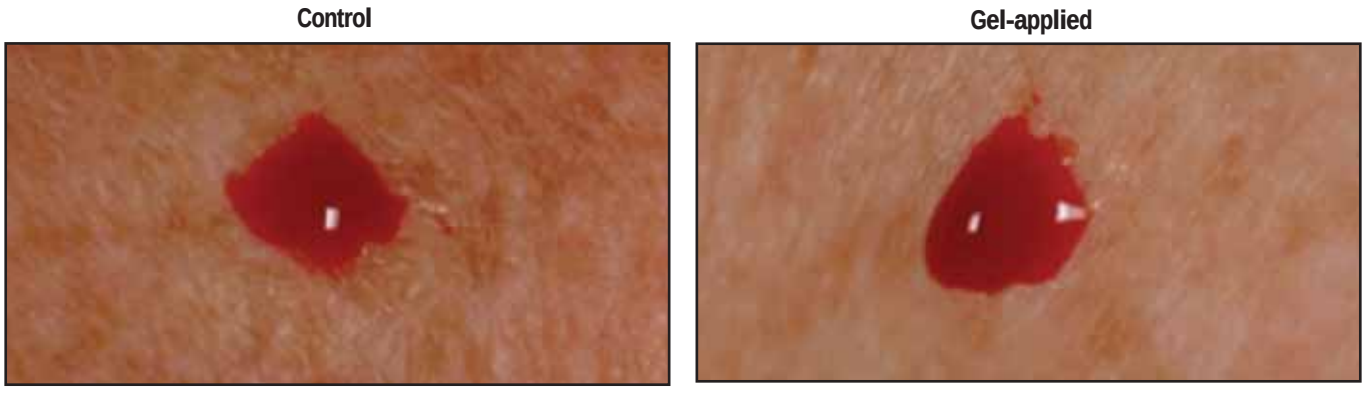


**Figure 3A.** Post-surgery (study Week 0)


**Figure 3B.** Pre-application baseline (study Week 2)

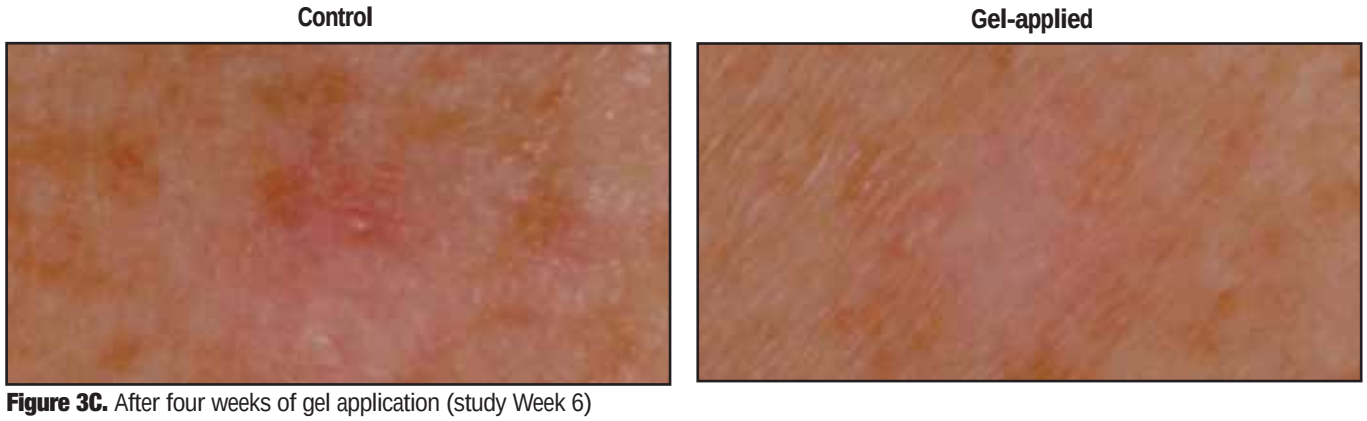


**Figure 3C.** After four weeks of gel application (study Week 6)

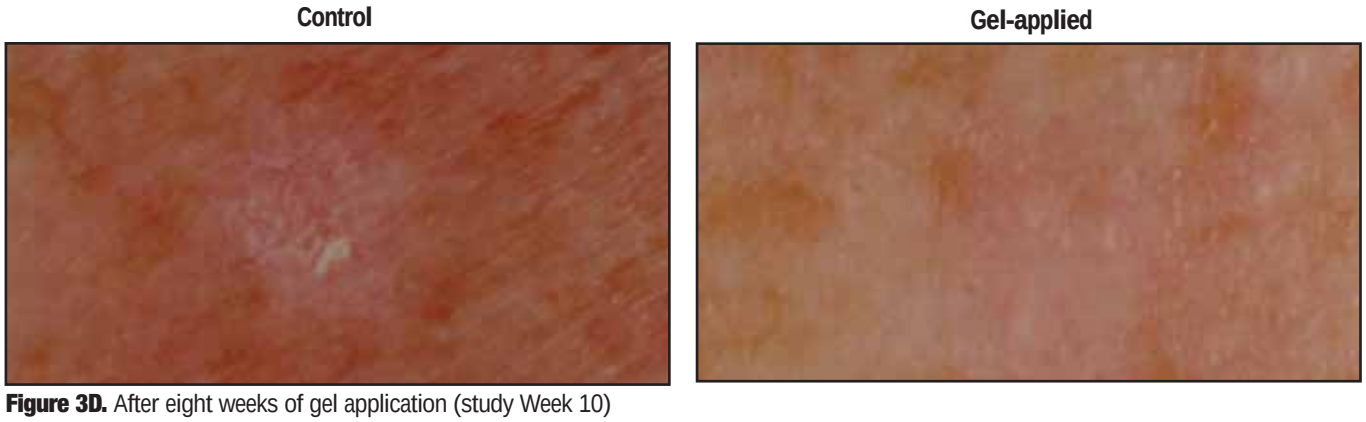


**Figure 3D.** After eight weeks of gel application (study Week 10)

The mechanisms underlying the beneficial aesthetic effect of onion extract on scar appearance are unknown and are beyond the scope of this study. There is substantial evidence that the bioflavenoid and metalloproteinase constituents of onion extract gel play a major role in reducing new scar formation.[5,7,11] The design of this study did not permit direct comparison of the vehicle gel alone. However, the vehicle contains no hydrating or moisturizing agents, such as allantoin, which could contribute to scar softness and appearance.[13]

The formulation of Mederma® Advanced Scar Gel differs from existing products in the following two ways: 1) the once-daily gel contains a higher concentration of onion extract than the original gel formula and 2) a proprietary liposomal skin penetrator system has been added. Aesthetic benefits in improvement of scar appearance from application of the new advanced onion extract gel formulation were achieved with only one application per day for eight weeks. The once-daily application provides patients with a more convenient application regimen than the previous onion extract formula and other products that require multiple (3x) daily applications for as long as 4 to 6 months to obtain results.

In conclusion, the results of this study demonstrate that once-daily application of the proprietary advanced formulation of onion extract gel is safe for use on new scars and significantly improves their overall appearance, redness, softness, and smoothness compared to control scars. In the majority of subjects, these benefits are apparent within 2 to 4 weeks of daily application and are fully defined after eight weeks of application of advanced onion extract gel.

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